IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	ARONHIME *et al.*
Serial No.	:	09/841,025
Filed	:	April 24, 2001
For	:	ZOLPIDEM HEMITARTRATE
Examiner	:	C. Chang
Art Unit	:	1625

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Commissioner for Patents
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Date: May 25, 2006
Signature: Shawn Huang

Declaration Under 37 C.F.R. § 1.132

I, Professor Gautam R. Desiraju, Ph.D., hereby state and declare the following:

1. I have been retained by Kenyon & Kenyon LLP, counsel for Teva Pharmaceuticals Inc. ("Teva"), the assignee of all right, title, and interest in U.S. application Serial No. 09/841,025.

I. QUALIFICATIONS

2. I am Professor of Chemistry at the University of Hyderabad since 1990.

3. I have been employed as a faculty member at the University of Hyderabad since 1979, first as a lecturer in 1979, then as a Reader in 1984, and then as professor since 1990. My duties include performing or supervising the analysis of chemical compounds using solid state characterization analytical techniques and instrumentation, such as single crystal X-ray diffraction, powder X-ray diffraction, thermal gravimetric analysis, differential scanning calorimetry, and hot stage microscopy.

4. I received a bachelor's in science degree from the University of Bombay in 1972. I received a Ph.D. from the University of Illinois at Urbana-Champaign in 1976 under the supervision of Professor David. Y. Curtin and Professor Iain C. Paul.

5. I have published over 275 papers in the area of crystal engineering and solid-state supramolecular chemistry. I am a well known author and have published books such as "Crystal Engineering - The Design of Organic Solids" published in 1989. I am co-author of "The Weak Hydrogen Bond in Structural Chemistry and Biology" (Oxford University Press, ISBN-13: 978-0-19-850970-7) first published in 1999. I am currently co-editor Acta Crystallographica, a journal reporting fundamental advances in all areas of crystallography including experimental and theoretical studies of the properties and arrangements of atoms, ions and molecules in condensed matter, and the theoretical and experimental aspects of the various methods to determine these arrangements. I am also a member of the editorial advisory board of Crystal Growth & Design a journal publishing articles on the physical, chemical, and biological phenomena and processes related to crystal growth and design of new materials. I am also a member of the editorial advisory board of CrystEngComm and a consulting editor of Accounts of Chemical Research.

6. I am a fellow of the Indian Academy of Sciences, the Indian National Academy of Sciences, the National Academy of Sciences (India), the Third World Academy of Sciences, and the Royal Society of Chemistry. And, I am a member of the executive committee of the International Union of Crystallography.

7. My effort in the field of crystallography has been recognized. Among the numerous awards I have received include the CHEMITO award, the Millennium Medal of the Indian Science Congress and the Silver Medal for Excellence in Research of the Chemical Research Society of India. I am also a recipient of the Humbolt Research Award; the Third World Academy of Sciences Award in Chemistry (2000); the Ranbaxy

Research Award (2000); the Priyadaranjan Ray Memorial Award of the Indian Chemical Society (2002); and the K. Anji Reddy Award for Innovation of the Indian Institute of Chemical Engineers (2002).

8. A copy of my *curriculum vitae* that summarizes my education, work history, awards, and honors is attached as Exhibit A.

II. MATERIALS REVIEWED

9. I have reviewed what I understand to be the specification of U.S. patent application Serial No. 09/841,025 ("the '025 application") and what I understand to be the Office Action mailed March 17, 2006 ("the Office Action"). I see that claim 161, as amended, reads: "Zolpidem hemitartrate Form D characterized by an X-ray powder diffraction pattern having peaks at about 7.1, 9.5, 14.1, 19.6 and 24.5 ± 0.2 degrees two-theta, and the corresponding d-spacing values of about 12.5, 9.3, 6.3, 4.53, and 3.63 Å." I will refer to the compound as "zolpidem hemitartrate" and to the specific solid state as "Form D."

10. I also attended the interview with Examiner Celia Chang on April 5, 2006, with Patrick Birde, King Lit Wong, Payam Moradian, Galit Gonen-Cohen, and Judith Aronhime, where the patentability of the claims was discussed.

III. IN THE CONTEXT OF THE '025 APPLICATION, ONE OF SKILL IN THE ART WOULD READILY UNDERSTAND THE CLAIMS TO BE DEFINITE.

10. I note that on page 2 of the Office Action the examiner states "[i]t is very confusing as to what is the scope of the claims." I disagree. The designation of zolpidem hemitartrate Form D in conjunction with the 5 powder x-ray diffraction (PXRD) peaks identifies a unique solid-state (crystalline) form of zolpidem hemitartrate. Thus, it is my opinion that the claim language identifies the crystalline zolpidem hemitartrate Form D in a manner so that a person skilled in the art reading the claims would be able to identify and distinguish the zolpidem hemitartrate Form D product according to the teachings of

the '025 application over other forms of zolpidem hemitartrate for at least the following reasons.

11. In my opinion, in 2000-2001 a person of ordinary skill in the art, to which the application pertains, would have been a person having a Ph.D., master's degree, or bachelor's degree in chemistry, medicinal chemistry, or a related field with several years of experience in solid state chemistry, or a person with equivalent knowledge from experience in the field. The person of ordinary skill in the art would also have had knowledge and background on polymorphs of pharmaceuticals, including methods of their preparation.

12. While there is no generally accepted convention for naming new crystalline forms of a compound, when a material exists in different crystalline forms the use of the term "Form" with an additional descriptor (an alphanumerical or descriptive designation) is a common method for naming particular crystal forms. In the scientific literature, it is common to find the report of a newly discovered crystalline form in which the author describes the procedure used to make the new crystalline form, names that crystalline form according to this method, and associates that name with sufficient characterizing physical data, such as powder x-ray diffraction, infrared absorption, hot stage microscopy, and/or differential scanning calorimetry, among others, to allow subsequent investigators to identify that new crystalline form and distinguish it from other crystalline forms of the same molecule.

13. Thus, in the field of crystal chemistry, it is common to see a particular crystalline form of a compound referred to by the chemical name, in this case zolpidem hemitartrate, followed by a descriptor such as the term "Form D." The skilled artisan readily understands that a term such as "zolpidem hemitartrate Form D" identifies a particular crystalline form of zolpidem hemitartrate. This understanding is reinforced by

the subsequent recitation of the claim. Claim 161 further reassures the skilled artisan of the crystalline form by enumerating five (5) PXRD peaks each of a specific value.

14. The existence of different crystalline forms of a compound is a crystallographic phenomenon. The diffraction pattern, such as a PXRD, is a primary tool used by scientists to investigate the crystallographic properties of solids. Based on my experience, one of skill in the art of solid-state chemistry would use x-ray diffraction to determine the physical characteristics of a crystalline compound.[1]

15. When a skilled artisan sees the term "zolpidem hemitartrate" further defined by five (5) PXRD peaks of 7.1, 9.5, 14.1, 19.6 and 24.5 ± 0.2 degrees two-theta and the corresponding d-spacing values of about 12.5, 9.3, 6.3, 4.53, and 3.63 Å, where the PXRD is a definitive physical analytical technique, the skilled artisan understands the definiteness and scope of the claim. The skilled artisan understands the term to encompass the chemical compound zolpidem hemitartrate, *i.e.*, a salt of two molecules of zolpidem per one molecule of tartaric acid. The skilled artisan understands the term to encompass a solid form of the zolpidem hemitartrate. And the skilled artisan further understands the term to encompass a solid form of the zolpidem hemitartrate with five (5) distinctive peaks in the powder x-ray diffractogram. Thus, the term conveys to the skilled artisan a unique crystalline form of zolpidem hemitartrate.

16. The skilled artisan would know that the five (5) PXRD peaks to be distinctive of zolpidem hemitartrate. The skilled artisan also would know that the peaks would characterize this particular zolpidem hemitartrate over other solid-state forms of zolpidem hemitartrate molecules.

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[1] In fact, one widely known author has stated "X-ray diffraction is perhaps the 'gold standard' for the qualitative determination of crystallinity. Not only can the presence of a crystalline phase be confirmed, but since each polymorph produces a **unique** diffraction pattern, the question of which polymorph crystallized can be addressed." Harry G. Brittain, "Polymorphism in Pharmaceutical Solids," pp. 398-399 (Marcel Dekker Inc., 1999)

17. Contrary to the Office Action's assertions, a review of the application itself demonstrates that each 5 x-ray diffraction peak pattern distinguishes one polymorph over the another. After a review of the solid-state forms of zolpidem hemitartrate in the '025 specification, the skilled artisan immediately notices distinguishing features among the characterizing PXRD patterns. After simple comparison of the zolpidem hemitartrate forms, the skilled artisan would know that only zolpidem hemitartrate Form D has the five recited peaks and that no other form has the same five peaks. Thus, the skilled artisan would know that the recited five (5) PXRD peaks define a unique form of zolpidem hemitartrate.

18. Further, when a skilled artisan views the '025 application as a whole, the skilled artisan understands that the crystalline zolpidem hemitartrate Form D defined by five (5) PXRD peaks is a crystalline structure independent of a solvent molecule. The skilled artisan also understands that if a solvent molecule was associated with a zolpidem hemitartrate molecule in the crystal lattice, then the PXRD would change to a PXRD different than the PXRD of a crystalline form of zolpidem hemitartrate not associated with a solvent molecule within the crystal lattice.

19. In my opinion, the likelihood that a second solid-state form of zolpidem hemitartrate would share the same five (5) peaks in the PXRD is highly unlikely. In my experience the likelihood that two zolpidem hemitartrate solid-state forms would share one peak is approximately 16.4%. Further, the likelihood of a crystalline zolpidem hemitartrate sharing two, three, four, or five peaks is 2.8%, 0.5%, 0.1%, and 0.05%, respectively. Accordingly, the description of zolpidem hemitartrate Form D with the five (5) characterizing PXRD peaks is highly definitive of one particular solid-state form of zolpidem hemitartrate.

20. The X-ray diffraction general test <941> of United States Pharmacopeia 23 edition (1995) describes a general method of identifying an unknown compound by comparing the x-ray diffraction of a known compound. The skill artisan understands that this method is a starting point for an analysis, and may be altered dependent upon the particular circumstances of the sample. In the case of zolpidem hemitartrate, the comparison of the ten most intense peaks is overkill because after the comparison of five (5) peaks, the skilled artisan can readily distinguish a first crystalline form of zolpidem hemitartrate from a second crystalline form. The analysis in paragraph 17 above clearly demonstrates that for zolpidem hemitartrate the skilled artisan need only consult the five (5) recited peaks to unequivocally establish the identity of crystalline Form D over other known forms. Thus, in my opinion one of skill in the art would not view the USP as requiring a comparison of at least ten reflections to distinguish two known compounds regardless of the particular circumstances of each crystalline form.

21. Thus, in my opinion one of skill in the art would as a matter of routine determine that the claim encompassed a molecule of zolpidem hemitartrate. Further, as a matter of routine, the skilled artisan would obtain a PXRD of another molecule of zolpidem hemitartrate. Finally, as a matter of routine, the skilled artisan would then compare the pattern obtained by PXRD with that recited in claim 161 to determine if the pattern contained the five (5) PXRD peaks recited in the claim. For at least these reasons, it is my opinion that one of skill in the art reading the phrase "Zolpidem hemitartrate Form D characterized by an X-ray powder diffraction pattern having peaks at about 7.1, 9.5, 14.1, 19.6 and 24.5 ± 0.2 degrees two-theta, and the corresponding d-spacing values of about 12.5, 9.3, 6.3, 4.53, and 3.63 Å" in light of the '025 specification would unequivocally understand the scope of the claim and differentiate the claimed form over other solid-state forms.

22. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and believe are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Gautam R. Desiraju

Dated: May 9, 2006

Gautam R. Desiraju, Ph.D.